

Therapeutic Ultrasound on Tumors

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Editorial

Tumor is one of the most serious diseases that threaten human health. The traditional therapeutic methods for tumors include surgical resection, radiotherapy, and chemotherapy. However, even if the application of the method above mentioned, some kinds of tumor are easy to relapse or metastasis [1]. Therefore, it is essential to find new treatment methods. Presently, ultrasonic irradiation for tumors, a non-invasive treatment, attracts scientists' attention [2]. The following is the most commonly used two kinds of ultrasonic method.

The first one is High Intensity Focused Ultrasound (HIFU). It is said that HIFU has important role in modern medical technology [3]. It is even considered to be one of the mature technologies of anti-cancer therapy [4]. The main mechanism of HIFU is that high intensity Ultrasound (US) wave focused on the target area of tumors produced high temperature (more than 45°C) in a short time, and let the temperature within the local target area increase rapidly, resulting in cell apoptosis or necrosis of the targeted area [5].

Focused ultrasonic wave of HIFU has good directivity, penetration and focus on biological tissue. Ultrasonic energy concentrated to the tumor tissue and destructed *in vitro* cancer cells, through accurate physical position, leads to coagulation necrosis of the tumor tissue. And finally the targeted tumor loses the ability of proliferation, invasion and metastasis.

Recent research found that when tumor tissue was destroyed by HIFU, the dying cancer cells may continuously release antigens, thus stimulate the patient to produce antitumor materials [6]. The increased immune system contributes to decrease the systemic micro-metastasis to some extent. In general, this enhanced immunity to human may reduce tumor recurrence and metastasis [7].

HIFU kills cancer cell by high temperature, destroys nourished vessel to cancer cell, and increases immunity system of patients. These three mechanisms increase abilities of tumor destruction and micro-metastasis. Active treatment of tumors from local areas combined with systemically chemotherapy, so as to achieve an ideal effect.

HIFU uses ultrasonic heat to kill tumor cells, similar to burn ants with a magnifying glass in the sun. Chemotherapy uses a variety of chemical drugs to kill tumor cells through different mechanisms, such as alkylation agent, anti-metabolism drugs, platinum complexes and so on. HIFU is often combined with chemotherapy as HIFU focused on one point to kill tumor cells quickly, but it is unable to kill tumor cells which have invaded and metastasized to other organs, in which, systemic chemotherapy could make up for deficiencies [8].

The second one is low-frequency ultrasound. Low frequency US is a new therapy for tumor treatment highlighted in recent years. The research of low-frequency US is still on the experimental stage. The biological effects of low frequency ultrasound include thermal effect, mechanical effect and cavitations effect. Due to the lower frequency (20-100 KHz), compared with high frequency (1-3MHz) in diagnostic US, lower intensity, less energy attenuation, and less absorbed heat by tissues lead to negligible temperature changes. So the most important effect of low-frequency ultrasound is cavitations effect [9].

Cavitations effect refers to the kinetic process of the micro-bubbles in liquids excited in the sound field, including vibration, continuous expansion, contraction, and finally collapse action [10].

In vitro studies revealed that low frequency ultrasound can induce the apoptosis of tumor cells, and then inhibit the proliferation of tumor cells [11].

The other researches demonstrated that micro bubbles can enhance the apoptosis effects of tumor cells induced by low frequency US. *in vivo* studies also disclosed that low frequency US can damage the angiogenesis of tumors and inhibit tumor growth [12]. Ultrasonic cavitations effects could cause mechanical injury on basilar membrane of micro-vessel, fracture of tumorial endothelial cells, collagen exposure, resulting in micro thrombosis, embolism or local blocking blood circulation, decreased blood supply. As a result, inhibited tumor angiogenesis led to micro vessel density decrease, local tumor cell death, tumor volume decrease, and finally achieved the purpose of cancer therapy [9,13].

Human prostate cancer xenografts in nude mice and New Zealand rabbits with hepatic VX2 tumors were treated by low-frequency US combined with micro bubbles. Results showed that the tumor growth was significantly inhibited [14]. Tumor cell apoptosis, vascular endothelial cell wall rupture, widened endothelial cell gaps, interstitial erythrocyte leakage, and micro vascular thrombosis were found on transmission electron microscopy. VEGF and COX-2 protein expression on endothelial cells and cytoplasm significantly decreased using immunohistochemistry [9].

Tumor cells apoptosis induced by low frequency ultrasound combined with micro bubbles has been confirmed by many *in vitro* and *in vivo* studies. However, many parameters, such as the optimum ultrasonic irradiation frequency, intensity, irradiation time, micro bubbles type and concentration, *et al.* remain to be further studied. The preliminary results revealed that low-frequency ultrasound combined with micro bubble has great potential effects on anti-cancer treatment, and provides a new alternative approach for clinical treatment of tumors.

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